

Literature Review on the State of Alzheimer's Disease Research

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- **Basic Science**

In the National Institutes of Health (NIH) 2013-2014 Alzheimer's Disease Progress Report, they describe various research advances in basic science, in a chapter titled, "Untangling Alzheimer's Biology". Various research studies published in 2013 investigated the brain hallmarks of Alzheimer's, including amyloid beta protein deposits which disrupt cellular communication, chemically-modified tau protein which leads to tangles and cell death, and other toxic proteins.

- 1) Using brain imaging techniques, researchers at Washington University in St. Louis confirmed that individuals with a genetic mutation resulting in early-onset, familial Alzheimer's produce 20 percent more amyloid beta in their brain when compared to their siblings who didn't inherit the mutation.
- 2) Researchers at Rush Alzheimer's Disease Center in Chicago found that in a group of 856 people, over half of the cases of cognitive decline were caused by some unexplained mechanisms other than the most common causes of dementia such as Alzheimer's disease, cerebrovascular disease, and Lewy body disease which together only accounted for 41 percent of cases. This study calls for more research into disease pathways leading to cognitive decline and mild cognitive impairment.
- 3) One of the possible disease pathways resulting in cognitive decline was also researched and described by the Rush Alzheimer's Disease Center team. The accumulation of a protein, transactive response DNA-binding protein 43 (TDP-43), was associated with faster cognitive decline in a group of 130 research volunteers. The protein was found in almost half of the group and is also a hallmark of frontotemporal dementia and amyotrophic lateral sclerosis (ALS).
- 4) Researchers at Massachusetts General Hospital in Boston inserted a mutant form of the human tau gene into a mouse model of Alzheimer's disease and were able to turn the gene "off" or "on" using a drug. When "on" the mice developed neurofibrillary tangles and brain cell degeneration like that seen in the Alzheimer's brain but when the gene was turned off, the

tangles disappeared and neurodegeneration was partially reversed. This suggests that drugs targeting abnormal tau protein may reverse pathology and symptoms of the disease.

- 5) Researchers at the University of Southern California crossbred two mouse models to create a new strain of mutant mouse that developed both Alzheimer's disease pathology and had fewer supportive cells (called pericytes) surrounding and protecting its blood vessels, transporting nutrients and waste between the blood and fluid surrounding the brain. These mutant mice developed worse learning and memory problems and more Alzheimer's disease brain hallmarks, demonstrating the vital role that blood-vessel associated cells play in clearing toxic proteins from the brain and identifying a new therapeutic target.ⁱ

- **Epidemiology: Risk and Protective Factors/Preventative Measures**

World Alzheimer's Report 2014

"The World Alzheimer's Report 2014, Dementia and Risk Reduction: An Analysis of Protective and Modifiable Risk Factors", was published in September 2014 and examines the evidence for modifiable risk factors for dementia. These risk factors include developmental, psychological and psychosocial, lifestyle, and cardiovascular factors. Low education in early life, hypertension in midlife, and smoking and diabetes across the lifespan were identified as the strongest risk factors associated with dementia. The report describes the potential impact that various interventions could have on dementia including—expanding access to secondary and post-secondary education; improved detection and treatment of hypertension and diabetes; increased physical activity and reduction in obesity; smoking cessation; and cognitive activity and stimulation in later life.

The World Alzheimer's Report acknowledges that research should focus on testing and establishing the benefits of these interventions through randomized controlled trials where feasible and through other sources of evidence, such as observational studies, when a randomized controlled trial is not applicable. The report also strongly encourages public health messaging efforts regarding brain health promotion, anti-tobacco, and non-communicable disease awareness and prevention strategies to improve global public health.

The World Alzheimer's Report reviewed the evidence from a number of research studies and noted that more research and clinical trials are needed to 1) establish the relationship between depression, anxiety disorders, psychological distress, and sleep disturbances and dementia 2) the association of diet and nutrients with cognitive function, impairment, and dementia.ⁱⁱ

The Alzheimer's Association International Research Grant Program is funding several new projects that look at non-drug, lifestyle-related interventions for dementia. Three studies announced in October 2014 include 1) a 12-week study, led by researchers at UC San Diego, investigating the impact of exercise, cognitive stimulation, or a combination of the two on lowering the risk for cognitive decline and dementia; 2) an evaluation, led by researchers at the Joslin Diabetes Center in Boston, into the impact of

aerobic training on the brain and thinking abilities in individuals with Type 2 diabetes; 3) a study, led by researchers at the University of Oklahoma Health Sciences, investigating the practice and learning of repetitive tasks for improving daily life skills and delaying the decline of life skills in individuals with dementia.ⁱⁱⁱ

- **Biomarkers and Early Detection**

Biomarkers

The NIH 2013-2014 progress report highlights the use of biomarkers—proteins in blood or cerebrospinal fluid or brain imaging of proteins—to advance the tracking of Alzheimer’s disease progression. The model for disease progression proposed that amyloid plaque deposits preceded tau protein changes and malformation in the brain. However, a study published in 2013 found that changes in tau protein preceded changes in amyloid protein but that changes in amyloid occur faster, are detected first, and may exacerbate the changes and destructive effects of abnormal tau. Using brain imaging techniques, researchers at the Mayo Clinic found that amyloid levels build up slowly in the brain over an average period of 15 years, indicating a wide window of opportunity for potential anti-amyloid interventions.

Researchers at the University of Washington School of Medicine investigated four biomarkers—brain imaged amyloid and amyloid, tau protein, and abnormal tau protein in cerebrospinal fluid—and their impact on cognition in over 200 cognitively normal volunteers (age 45-88) observed for up to 7.5 years and found that levels of the biomarkers predicted who would develop cognitive decline and memory loss. The results also uncovered health disparities based on age, gender, and race, with older individuals, men, and African-Americans experiencing faster cognitive decline.^{iv}

Detection

The NIH 2013-2014 progress report highlights a couple of advancements in the detection of Alzheimer’s disease. Researchers at the National Institute of Radiological Sciences in Japan and at the University of Pennsylvania tested a series of tracer compounds that can label abnormal tau protein in a mouse model of AD. A sensitive tracer compound (PBB3) was detected and used in brain imaging studies using six volunteers, three of which had Alzheimer’s. The fluorescent tracer was highly visible in areas of the brain known to be affected by Alzheimer’s in the three individuals living with the disease and in another individual living with a disorder that also results in abnormal tau formations. The results demonstrate that the compound can label abnormal tau in the living brain and may help distinguish between different forms of dementia and allow for the testing of drug therapies that target abnormal tau.

Researchers at the University of Rochester Medical Center studied navigation by observing eye and head movements in young people, older people with normal cognition, and in individuals living with early Alzheimer’s disease. Compared to the younger group, older individuals were slower in response to moving patterns and individuals with Alzheimer’s disease had diminished responses, indicating that

visual response times could be used to develop a test to distinguish between normal aging and early AD.^v

- **Health Disparities**

Gender and Genetics

On October 29, 2014, the UK Government announced that dementia is the leading cause of death among women in England and Wales, according to the Office for National Statistics. The ONS attributes this to the trend of people living longer, women living longer than men, and a better understanding of dementia resulting in doctors being more likely to list dementia as a cause of death. Dementia was the third leading cause of death for men, with ischemic vascular disease (IVD) being the most common cause of death among men.^{vi} Interestingly, IVD is also the second most common cause of dementia.^{vii} Hilary Evans, director of external affairs for Alzheimer's Research UK, said: "The figures highlight dementia as a huge problem that we cannot shy away from any longer... We must now turn our attentions to dementia - our greatest health challenge - and invest in research that will drive better prevention and treatment of the condition."

Dr. Andre Altman and colleagues at Stanford University published a study in April 2014 that looked at the effect that sex and a genetic risk factor for sporadic Alzheimer's disease has on the progression of the disease from healthy aging to MCI or AD and from MCI to AD, concluding a greater risk for developing AD in women who carry the *APOE4* gene and an association with AD brain pathology. This study proposal used the National Alzheimer's Coordinating Center Research Database.^{viii}

The NIH 2013-2014 progress report highlighted research conducted at the University of Washington's School of Medicine. This study investigated the safety and effectiveness of treating memory loss associated with MCI or AD using an insulin nasal spray. In a randomized controlled trial involving 104 older volunteers with MCI or AD, results show that both men and women showed improvement in memory following the nasal spray treatment, however men needed a higher dose (40 versus 20 International Units of Insulin). At the higher dose of the spray, men who were negative for the *APOE4* gene improved but women who were negative for the gene worsened. Individuals who were positive for the *APOE4* gene remained cognitively stable.^{ix}

Ethnicity/Race

There are a number of proposals within the National Alzheimer's Coordinating Center Research Database that are investigating disparities among our state and nation's diverse populations. For example, researchers at California State University Northridge are proposing a longitudinal study focusing on the age of onset, age of diagnosis, treatment of dementia, and participation in research among African Americans and Latinos.^x Researchers at the University of Southern California propose to measure, track, and compare cognitive decline among a sample of older Asians, African-Americans,

Latinos, and Whites over time and discuss possible interventions to mitigate the decline in diverse populations.^{xi}

The NIH 2013-2014 progress report cited three research studies published in 2013 that aim to investigate the variable risk for cognitive decline and dementia among certain racial, ethnic, and socioeconomic groups.

- 1) Researchers at the Alzheimer's Disease Genetics Consortium and Columbia University Medical Center analyzed genetic data from nearly 6,000 participants age 60 and older and found an increased risk for developing Alzheimer's disease among African-Americans who expressed a form of a gene called *ABCA7*, which plays a role in cholesterol and lipid metabolism. While the risk doubled for African-Americans, the risk was an increase of only 10 to 20 percent among Whites, indicating different risk profiles for late-onset Alzheimer's.
- 2) Researchers at the North Texas Science Center analyzed data from over 1600 older individuals of non-Hispanic or Hispanic descent and found that both groups had similar rates of mild cognitive impairment, with age as the greatest risk factor. However, Mexican Americans experienced cognitive impairment earlier (10 years younger) than the non-Hispanic group and were not protected by higher levels of education. Diabetes also did not confer a greater risk among Mexican Americans, indicating that more research is needed to understand the risk factors associated with MCI among Latinos.
- 3) Researchers at UCSF investigated the impact of diabetes on dementia and cognitive impairment risk among over 1600 older participants from the Sacramento Area Latino Study on Aging, whose blood sugar and cognitive function was tracked for up to 10 years. Participants with diabetes had a two-fold increase for developing dementia or cognitive impairment without dementia. Mexican Americans with diabetes were at increased risk, whether their diabetes was treated or not, suggesting that preventing diabetes onset could reduce future rates of dementia among this population.^{xii}

- **Drug Therapies and Other Treatments**

The NIH 2013-2014 progress report highlights a number of clinical drug trials aimed at preventing dementia, treating dementia, or targeting psychiatric symptoms; and non-drug approaches for treatment.

Trials aimed at preventing dementia include testing anti-amyloid drugs in volunteers who carry a mutation for early-onset Alzheimer's but who do not yet have symptoms or have mild symptoms; testing an anti-amyloid drug in symptom-free volunteers who have abnormally high levels of amyloid detected by brain scans; testing an experimental drug in a family with rare, early-onset Alzheimer's; and testing an anti-amyloid drug in cognitively normal older volunteers who carry two copies of the *APOE4* allele (form of the gene) which confers a higher risk for developing AD.

Trials aimed at targeting psychiatric symptoms include the Alzheimer's Disease Cooperative Study's investigation into how a high blood pressure drug impacts agitation symptoms in AD patients; the Houston, Texas-based Veteran Affairs Health Services Research and Development Service's Peaceful Mind Therapy program (based on cognitive behavioral therapy such as deep breathing and self-talk) and its impact on anxiety in people with dementia; and the Medical University of South Carolina's use of a drug to treat apathy, the loss of interest and motivation in daily activities in the absence of depression.

Trials using non-drug approaches for treatment include a study conducted by researchers at UCSF which used a specialized brain training game to improve cognition, attention, and memory in older people; and a study conducted at the University of Iowa that investigated the impact of exercise on cognition and the brain's white matter (nerve tissue important for cellular communication), which found that aerobic exercise may improve cognition and white matter integrity in older people.^{xiii}

- **Caregiving**

The NIH 2013-2014 progress report highlights two research studies published in 2013 in the section on "Caregiving and Alzheimer's Disease".

- 1) Researchers at the Hebrew Senior Life Institute for Aging Research in Boston interviewed 345 older women caregivers over 10 years, one-third of whom were caring for someone with dementia. One in five (22.8 percent) of those caring for someone with dementia had high depressive symptoms, which was twice the rate of that found in caregivers of people with other disorders (11.2 percent). The higher levels of depression were influenced by feeling trapped because of the greater demands of caring for someone with dementia and the disruptive behavior of those with Alzheimer's. These reported feelings indicate that alleviating caregiver burden and targeting problematic behavior may alleviate the risk and incidence of depression among caregivers.
- 2) Researchers at Pennsylvania State University investigated the impact of Adult Day Services on caregiver stress, emotions, and health. 173 caregivers were interviewed during eight consecutive days. The caregivers reported that on the days that they used adult day services, they experienced respite from the day-to-day stress of caregiving, reduced feelings of anger, and other positive experiences despite feeling more non-caregiving related stress (i.e. work-related stress). Interestingly, caregivers reported more health symptoms on the days that adult day services were used and the researchers believe that this is because caregivers had more time to focus on their own health concerns. The study suggests that adult day services can be protective against chronic caregiver stress.^{xiv}

- **Ongoing Clinical Trials**

The NIH lists 68 ongoing clinical trials in the 2013-2014 progress report. These clinical trials, expected to be completed between 2014 and 2019, are organized in five sections and include:

- 1) Alzheimer's Disease Presymptomatic/Primary Prevention Trials- includes nutritional, hormonal, cardiovascular, immunotherapy, exercise and other non-pharmacological approaches, and an antidepressant study.
- 2) Alzheimer's Disease/MCI Clinical Trials- includes nutritional, cardiovascular, hormonal, metabolic, exercise and other nonpharmacological approaches, and other interventions such as genetic, drug, and immunotherapy approaches.
- 3) Age-related Cognitive Decline Clinical Trials- includes cognitive training, Omega-3 fatty acids and antioxidants, active engagement, hormonal therapy, exercise, and exercise and cognitive training.
- 4) Delirium Prevention and Treatment Clinical Trials- includes studies focused on understanding and preventing post-operative delirium.
- 5) Alzheimer's Disease/MCI Neuropsychiatric Symptoms Clinical Trials- includes studies focused on drug treatment therapies to manage agitation and depression and to improve the function and behavior of nursing home residents with dementia.^{xv}

- **Multidisciplinary Approaches**

The National Institutes of Health announced in October 2014 that it was awarding over \$5 million to support multidisciplinary research projects investigating Frontotemporal Lobe Degeneration (FTD), a type of dementia that affects around 50,000 Americans. FTD is characterized by the loss of brain cells in the frontal and temporal lobes of the brain and can lead to changes in behavior, emotion, and difficulty with language and speaking.

The three, five-year projects will 1) track the medical, neurological, behavioral, and cognitive outcomes of families with heritable (i.e. genetic) FTD in order to identify biomarkers which will help determine effective therapeutic interventions; 2) establish a clinical research consortium to improve clinical trial design and identify new types of treatments for FTD; 3) use animal models, cell cultures, and human brain tissue to study a genetic mutation that is the most common cause of FTD and amyotrophic lateral sclerosis (ALS) in order to understand how the mutation leads to disease and develop therapies to mitigate the effects of the mutation.^{xvi}

In the United Kingdom, the Medical Research Council—in partnership with six companies—is investing £50 million in the Dementias Research Platform UK, to accelerate dementia research towards new treatments and interventions. The DPUK will be the largest population study ever, with two million

people over the age of 50 taking part in the study in various ways. DPUK will investigate lifestyle factors (i.e. education and physical activity) and their impact on dementia risk; collect and analyze DNA samples to identify differences which increase or decrease dementia risk or alter disease progression; use stem cells from individuals with inherited or early stage dementia to better understand why nerve cells die; and measure and track the medical and neurological outcomes of individuals in the early, preclinical stages of dementia in order to better diagnose and treat the condition.^{xvii}

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 - iii New Alzheimer's Association research grants fund multiple investigations of non-drug treatments
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 - iv National Institutes of Health, 2013-2014 Alzheimer's Disease Progress Report, "Biomarkers Track Alzheimer's Progression"
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 - x Longitudinal Study of Dementia among minority groups looking at the disparities
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